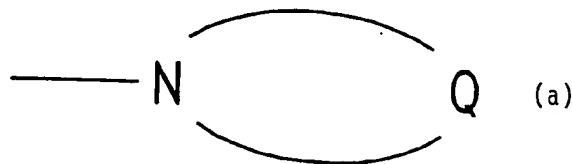
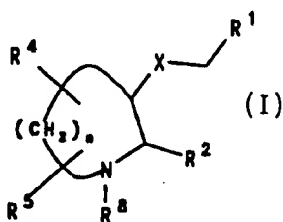




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 211/42, 401/12, 207/12 C07D 211/54, A61K 31/445 A61K 31/40	A1	(11) International Publication Number: WO 94/02461 (43) International Publication Date: 3 February 1994 (03.02.94)
(21) International Application Number: PCT/GB93/01525 (22) International Filing Date: 20 July 1993 (20.07.93) (30) Priority data: 9216065.4 28 July 1992 (28.07.92) GB 9216304.7 31 July 1992 (31.07.92) GB 9224918.4 27 November 1992 (27.11.92) GB 9226058.7 14 December 1992 (14.12.92) GB (71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB). (72) Inventors; and (75) Inventors/Applicants (for US only) : SEWARD, Eileen, Mary [IE/GB]; 15 The Colts, Thorley Park, Bishops Stortford, Hertfordshire CM23 4DL (GB). SWAIN, Christopher, John [GB/GB]; 8 Mangers Lane, Duxford, Cambridge CB2 4RN (GB).	(74) Agent: QUILLIN, Helen, Kaye; Merck & Co., Inc., European Patent Department, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). (81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	

(54) Title: AZACYCLIC COMPOUNDS**(57) Abstract**

Compounds of Formula (I), and salts and prodrugs thereof, wherein n is 1, 2 or 3; X represents O or S; R¹ is optionally substituted phenyl; R² is aryl or heteroaryl; R⁴ and R⁵ are independently H, halo, C₁₋₆alkyl, oxo, CH₂OR^a, CO₂R^a or CONR^aR^b; R⁸ represents C(COOR^a)₂, C(CONR^aR^b)₂ or C₁₋₆alkyl substituted by C(=NR^a)NR^bNR^cCO₂R^d, CONHNR^aR^b, C(S)NR^aR^b, CONR^aC₁₋₆alkylR¹², CONR¹³C₂₋₆alkynyl, CONR¹³C₂₋₆alkenyl, COCONR^aR^b, CONR^aC(NR^b)NR^cR^d, CONR¹³SO₂R^a, SO₂NR¹³COR^a, CONR^aheteroaryl or COR^a; R^a, R^b, R^c and R^d are each H, C₁₋₆alkyl, phenyl or trifluoromethyl. R¹² represents OR^a, CONR^aR^b or heteroaryl; R¹³ represents H or C₁₋₆alkyl; and R⁹ represents a group (a) where Q represents the residue of a non-aromatic azacyclic or azabicyclic ring system; are tachykinin antagonists useful in therapy.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NE	Niger
BE	Belgium	GN	Guinea	NL	Netherlands
BF	Burkina Faso	GR	Greece	NO	Norway
BG	Bulgaria	HU	Hungary	NZ	New Zealand
BJ	Benin	IE	Ireland	PL	Poland
BR	Brazil	IT	Italy	PT	Portugal
BY	Belarus	JP	Japan	RO	Romania
CA	Canada	KP	Democratic People's Republic of Korea	RU	Russian Federation
CF	Central African Republic	KR	Republic of Korea	SD	Sudan
CG	Congo	KZ	Kazakhstan	SE	Sweden
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovak Republic
CM	Cameroon	LU	Luxembourg	SN	Senegal
CN	China	LV	Latvia	TD	Chad
CS	Czechoslovakia	MC	Monaco	TG	Togo
CZ	Czech Republic	MG	Madagascar	UA	Ukraine
DE	Germany	ML	Mali	US	United States of America
DK	Denmark	MN	Mongolia	UZ	Uzbekistan
ES	Spain			VN	Viet Nam
FI	Finland				

- 1 -

AZACYCLIC COMPOUNDS

5 This invention relates to a class of azacyclic compounds, which are useful as tachykinin antagonists. More particularly, the compounds of the invention comprise an azacyclic ring system substituted by an arylmethyloxy or arylmethylthio moiety.

10 The tachykinins are a group of naturally-occurring peptides found widely distributed throughout mammalian tissues, both within the central nervous system and in the peripheral nervous and circulatory systems. The structures of three known mammalian tachykinins are as follows:

15 Substance P:

Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH₂

Neurokinin A:

His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH₂

Neurokinin B:

20 Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH₂

Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, 25 chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular 30 inflammatory diseases, proliferative vitreoretinopathy, irritable bowel syndrome and disorders of bladder function including cystitis and bladder detruser hyper-reflexia is reviewed in "Tachykinin Receptors and

- 2 -

Tachykinin Receptor Antagonists", C.A. Maggi, R. Patacchini, P. Rovero and A. Giachetti, J. Auton. Pharmacol. (1993) 13, 23-93. Tachykinin antagonists are also believed to be useful in allergic conditions

5 [Hamelet et al Can. J. Pharmacol. Physiol. (1988) 66 1361-7], immunoregulation [Lotz et al Science (1988) 241 1218-21 and Kimball et al, J. Immunol. (1988) 141 (10) 3564-9], and as anticonvulsants [Garant et al., Brain Research (1986) 382 372-8]. Tachykinin antagonists may

10 also be useful in the treatment of small cell carcinomas, in particular small cell lung cancer (SCLC) [Langdon et al., Cancer Research (1992) 52, 4554-7].

It has furthermore been suggested that tachykinins have utility in the following disorders:

15 depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex

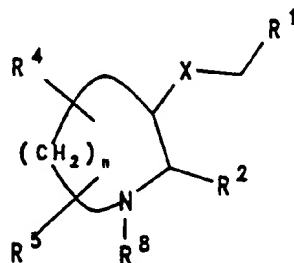
20 sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders related to immune enhancement or suppression such as systemic lupus erythmatosis (European patent application

25 no. 0 436 334), conjunctivitis, vernal conjunctivitis, contact dermatitis, atropic dermatitis, urticaria, and other eczematoid dermatitis (European patent application no. 0 394 989) and emesis (European patent application no. 0 533 280).

30 European patent application no. 0 436 334 discloses 4- to 7-membered azacyclic compounds substituted at the 3-position by a substituted amino moiety. The compounds are said to be tachykinin antagonists.

- 3 -

The present invention provides a compound of formula (I), or a salt or prodrug thereof:



(I)

wherein

n is 1, 2 or 3;

X represents O or S;

15 R¹ represents phenyl optionally substituted by 1, 2 or 3 groups selected from C₁₋₆alkyl, C₂₋₆ alkenyl, C₂₋₆alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, -OR^a, SR^a, SOR^a, SO₂R^a, -NR^aR^b, -NR^aCOR^b, -NR^aCO₂R^b, -CO₂R^a and -CONR^aR^b;

20 R² represents aryl selected from phenyl and naphthyl; heteroaryl selected from indazolyl, thienyl, furyl, pyridyl, thiazolyl, tetrazolyl and quinolyl; benzhydryl; or benzyl; wherein each aryl or heteroaryl moiety may be substituted by C₁₋₆alkyl, C₁₋₆alkoxy, halo or trifluoromethyl;

25 R⁴ and R⁵ may be present on any available carbon atom of the azacyclic ring and each independently represent H, halo, C₁₋₆alkyl, oxo, CH₂OR^a, CO₂R^a or CONR^aR^b;

30 R⁸ represents C(COOR^a)₂, C(CONR^aR^b)₂ or C₁₋₆alkyl substituted by C(=NR^a)NR^bNR^cCO₂R^d, CONHN^aR^b, C(S)NR^aR^b, CONR^aC₁₋₆alkylR¹², CONR¹³C₂₋₆alkynyl, CONR¹³C₂₋₆alkenyl, COCONR^aR^b, CONR^aC(NR^b)NR^cR^d, CONR¹³SO₂R^a, SO₂NR¹³COR^a, CONR^aheteroaryl or COR^q;

- 4 -

R^a , R^b , R^c and R^d each independently represent H, C_{1-6} alkyl, phenyl or trifluoromethyl.

R^{12} represents OR^a , $CONR^aR^b$ or heteroaryl;

R^{13} represents H or C_{1-6} alkyl; and

5 R^q represents a group



where Q represents the residue of a non-aromatic azacyclic or azabicyclic ring system.

15 As used herein, the definition of each expression, when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

The alkyl, alkenyl and alkynyl groups referred to with respect to the above formula may represent
20 straight, branched or cyclic groups, or combinations thereof. Thus, for example, suitable alkyl groups include methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and cycloalkyl-alkyl groups such as
25 cyclopropylmethyl; suitable alkenyl groups include vinyl and allyl; and suitable alkynyl groups include propargyl.

The term "halo" as used herein includes fluoro, chloro, bromo and iodo, especially chloro and fluoro.

30 The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible in vivo into the required compound of formula (I). Conventional procedures for the selection and

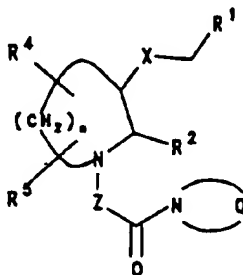
- 5 -

preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The compounds according to the invention may exist both as enantiomers and as diastereomers. In particular, the relative orientation of the 2- and 3-substituents on the azacyclic ring may give rise to cis and trans diastereoisomers, of which the cis stereochemistry is preferred. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

One subgroup of compounds according to the invention is represented by compounds of formula (I) wherein R^4 and R^5 each independently represent H, halo, C_{1-6} alkyl, oxo, CO_2R^{10} or $CONR^{10}R^{11}$; R^8 represents C_{1-6} alkyl substituted by a group selected from $CONHNR^aR^b$, $C(S)NR^aR^b$, $CONR^aC_{1-6}alkylR^{12}$, $CONR^{13}C_{2-6}alkynyl$, $CONR^{13}C_{2-6}alkenyl$, $COCONR^aR^b$, $CONR^aC(NR^b)NR^aR^b$, and $CONR^aheteroaryl$; and salts and prodrugs thereof.

A further subgroup of compounds according to the invention is represented by compounds of formula (Ia):



(Ia)

wherein n , X , R^1 and R^2 are as defined for formula (I); Q is the residue of an azacyclic or a bridged azabicyclic ring system;

- 6 -

Z represents an alkyl chain of 1, 2, 3, 4, 5 or 6 carbon atoms; and

R^4 and R^5 each independently represent H, halo, C_{1-6} alkyl, oxo, CO_2R^a or $CONR^aR^b$; and salts and prodrugs thereof.

Preferably n is 2 or 3, more preferably 3.

Preferably X represents O.

Preferably R^1 represents substituted phenyl.

When R^1 is substituted phenyl suitable substituents include nitro, trifluoromethyl, trimethylsilyl, bromo, chloro, fluoro, iodo, cyano, C_{1-6} alkyl such as methyl, ethyl, i-propyl, i-butyl, t-butyl and cyclopropyl, C_{2-6} alkenyl such as vinyl, C_{1-6} alkoxy such as methoxy, ethoxy and i-propoxy, phenoxy, amino, carboxamido and carbonylmethoxy. Preferably R^1 represents phenyl substituted by one or more groups selected from C_{1-4} alkyl, such as methyl and t-butyl, trifluoromethyl and halo such as iodo, bromo chloro and fluoro.

Suitably R^1 represents monosubstituted phenyl, such as 3-substituted phenyl or, preferably, disubstituted phenyl, such as 3,5-disubstituted phenyl. Preferably R^1 represents phenyl substituted at the 3-position by trifluoromethyl or a C_{1-6} alkyl group such as t-butyl, or 3,5-disubstituted phenyl wherein the substituents are independently selected from trifluoromethyl, chloro, fluoro, methyl and t-butyl. Particularly preferred is 3,5-bis(trifluoromethyl)phenyl.

Suitably R^2 represents benzhydryl or optionally substituted phenyl, such as phenyl optionally substituted by halo such as fluoro or chloro, preferably in the 3-position. Preferably R^2 represents unsubstituted phenyl or unsubstituted benzhydryl, more preferably unsubstituted phenyl.

- 7 -

Suitable values for R^4 and R^5 include H, C_{1-6} alkyl, especially methyl, hydroxymethyl and oxo. The substituents R^4 and R^5 may be located on any available carbon atom of the azacyclic ring including, except in the case where the substituent R^4 or R^5 in question represents oxo, C-2 and C-3. Preferably at least one of R^4 and R^5 represents H. In one preferred group of compounds R^4 and R^5 both represent H. In a further preferred group of compounds one of R^4 and R^5 is H and the other of R^4 and R^5 is methyl, preferably 2-methyl.

Suitable values for R^8 include $C(COO(C_{1-6}alkyl))_2$, such as $C(COOCH_3)_2$, $C(CONH_2)_2$ and $C_{1-6}alkyl$, preferably $C_{1-4}alkyl$, more preferably CH_2 or $CH(CH_3)$, substituted by $C(=NH)NHNHCO_2C_{1-6}alkyl$, $CONHNH_2$, $COCONH_2$, $CONHC(NH)NH_2$, $C(S)NH_2$, $CONR^{13}C_{2-6}alkynyl$, $CONR^aC_{1-6}alkylC_{1-6}alkoxy$, $CONHSO_2C_{1-6}alkyl$, $CONR^aC_{1-6}alkylheteroaryl$, $CONR^aheteroaryl$ or COR^q .

When R^8 represents $C_{1-6}alkyl$ substituted by $CONR^aC_{1-6}alkylheteroaryl$ or $CONR^aheteroaryl$, the heteroaryl moiety will suitably be selected from thienyl, furyl, pyridyl, thiazolyl, tetrazolyl, pyrrolyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, quinolyl, triazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, isothiazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, benzothiophenyl, benzofuranyl, and indolyl, preferably, furyl and pyridyl. The heteroaryl moiety may be optionally substituted. Suitable substituents include one or more of $C_{1-6}alkyl$, $C_{1-6}alkoxy$, phenyl, oxo, thioxo, halo, trifluoromethyl, NR^aR^b , NR^aCOR^b , $CONR^aR^b$, SR^a , SO_2R^a , CO_2R^a and CH_2OR^a , where R^a and R^b are as previously defined.

The non-aromatic azacyclic or azabicyclic ring system of which Q forms the residue may contain, in addition to the nitrogen atom through which the ring is

- 8 -

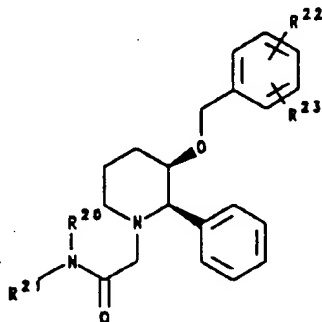
linked to the carbonyl moiety of the group COR^Q , a further heteroatom selected from O and S, or a group NR^{18} , where R^{18} is H or C_{1-6} alkyl.

When Q forms the residue of an azacyclic ring system, the azacyclic ring system will suitably contain from 5 to 9 ring atoms, preferably 5, 6 or 7 ring atoms, more preferably 6.

When Q forms the residue of an azabicyclic ring system, the azabicyclic ring system will suitably contain from 7 to 10 ring atoms, preferably 6 or 8 ring atoms, more preferably 8.

Suitable examples of the ring system of which Q forms the residue include pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, N-methylpiperazinyl azabicyclo[2.2.2]octanyl and azabicyclo[3.2.2]nonyl, preferably piperidyl, morpholinyl or N-methylpiperazinyl, more preferably morpholinyl or N-methylpiperazinyl.

A preferred subgroup of compounds according to the invention is represented by compounds of formula (Ib), and salts and prodrugs thereof.



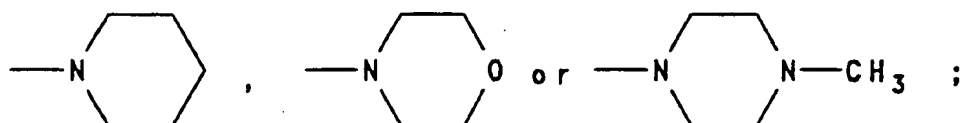
(Ib)

wherein

R^{20} represents H or C_{1-6} alkyl, preferably H or methyl;

- 9 -

R^{21} represents NH_2 , $C(=NH)NH_2$, C_{2-6} alkynyl or C_{1-6} alkyl substituted by C_{1-6} alkoxy, such as methoxy or heteroaryl, such as furyl or pyridyl; or R^{20} and R^{21} together with the nitrogen atom to which they are
 5 attached form a group



R^{22} and R^{23} independently represent H C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, OR^a , SR^a , SOR^a , SO_2R^a ,
 15 NR^aR^b , NR^aCOR^b , $NR^aCO_2R^b$, COR^a or $CONR^aR^b$, where R^a and R^b are as previously defined.

For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of
 20 the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound
 25 according to the invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, sulphuric acid, oxalic acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic
 30 acid or phosphoric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Thus, for example, when both R^1 and R^2 are other than hydrogen, the

- 10 -

nitrogen atom to which they are attached may be further substituted to give a quaternary ammonium salt.

Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

5 The present invention accordingly provides compounds of formula (I) and their pharmaceutically acceptable salts.

10 The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible in vivo into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

20 The compounds according to the invention may exist both as enantiomers and as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

25 The substance P antagonising activity of the compounds described herein was evaluated using the human NK1R assay described in published European patent application no. 0 528 495. The method essentially involves determining the concentration of the test compound required to reduce by 50% the amount of radiolabelled substance P binding to human NK1R, thereby affording an IC₅₀ value for the test compound. The compounds of Examples 1-10, for example, were found to have IC₅₀ values less than 100nM.

- 11 -

The invention also provides pharmaceutical compositions comprising a compound of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms
5 such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or topical administration including administration by inhalation or insufflation.

10 For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose,
15 sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When
20 referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and
25 capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise
30 compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by

- 12 -

an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be

- 13 -

administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

For topical administration, for example as a cream, ointment or lotion, pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or arylalkanols, vegetable oils, polyalkylene glycols, petroleum based jelly, ethyl cellulose, ethyl oleate, carboxymethylcellulose, polyvinylpyrrolidone, isopropyl myristate and other conventionally-employed non-toxic, pharmaceutically acceptable organic and inorganic carriers. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting agents, bodying agents and the like, as for example, polyethylene glycols 200, 300, 400 and 600, carbowaxes 1,000, 1,500, 4,000, 6,000 and 10,000, antibacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and which are non-injurious in use, thimerosal, methyl and propyl paraben, benzyl alcohol, phenyl ethanol, buffering ingredients such as sodium chloride, sodium borate, sodium acetates, gluconate buffers, and other conventional ingredients such as sorbitan monolaurate, triethanolamine, oleate, polyoxyethylene sorbitan monopalmitate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol, ethylenediamine tetraacetic acid, and the like.

The present invention further provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), which process comprises bringing a compound of formula (I) into association with a pharmaceutically acceptable carrier or excipient.

- 14 -

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity. These

5 may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as dementia, including senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating

10 diseases such as MS and ALS and other neuropathological disorders such as peripheral neuropathy, including diabetic and chemotherapy-induced neuropathy, and postherpetic and other neuralgias; small cell carcinomas such as small cell lung cancer; respiratory diseases,

15 particularly those associated with excess mucus secretion such as chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, and bronchospasm; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis,

20 osteoarthritis and rheumatoid arthritis; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atopic

25 dermatitis, urticaria, and other eczematoid dermatitis; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse immunological reactions such as rejection of transplanted

30 tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's

- 15 -

disease and incontinence; emesis, including acute, delayed and anticipatory emesis, for example, induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, surgery, migraine and variations in
5 intercranial pressure; disorders of bladder function such as bladder detrusor hyper-reflexia; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina,
10 migraine and Reynaud's disease; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

The compounds of formula (I) are particularly
15 useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteoarthritis, rheumatoid arthritis
20 and especially migraine.

The present invention further provides a compound of formula (I), or a salt or prodrug thereof, for use in therapy.

In the treatment of conditions involving
25 actions of tachykinins released physiologically in response to noxious or other stimuli, a suitable dosage level is about 0.001 to 50 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be
30 administered on a regimen of 1 to 4 times per day, preferably once daily.

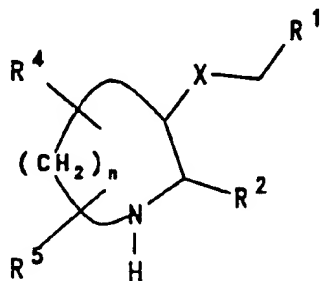
According to a further or alternative aspect, the present invention provides a method of treatment of a human or animal subject suffering from or susceptible to

- 16 -

a condition characterised by the presence of an excess of tachykinin which method comprises administering to a human or animal subject in need of such treatment an effective amount of a compound of formula (I), or a salt or prodrug thereof.

The present invention also provides the use of a compound of formula (I), or a salt or prodrug thereof, for the manufacture of a medicament for the treatment of conditions characterised by the presence of an excess of tachykinins.

According to one general process (A), the compounds according to the invention may be prepared by a process which comprises reacting a compound of formula (II):



(II)

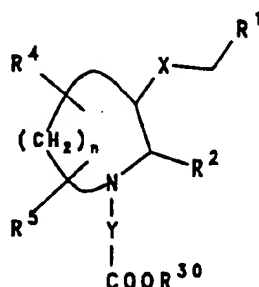
wherein R¹, R², R⁴, R⁵, X and n are as defined for formula (I) above, with a reagent suitable to introduce the group R⁸, for example, a halide or acyl halide, or corresponding mesylate or tosylate, of formula R⁸-L, where L represents halo, such as chloro, bromo or iodo, methylsulphonate or p-toluenesulphonate, or any other suitable leaving group, in the presence of a base.

Suitable bases of use in the reaction include inorganic bases such as alkali metal carbonates, for example, potassium carbonate.

- 17 -

Conveniently the reaction is effected in a suitable organic solvent, for example, dimethylformamide.

According to a second process (B), compounds of formula (I) wherein R^8 represents C_{1-6} alkyl substituted by
 5 $CONR^aC_{1-6}alkylR^{12}$, $CONR^{13}C_{2-6}alkenyl$, $CONR^{13}C_{2-6}alkynyl$,
 $CONR^aC(NR^b)NR^cR^9$, $CONR^aheteroaryl$ or COR^q may be prepared
 by reaction of an intermediate of formula (III):



(III)

wherein R^1 , R^2 , R^4 , R^5 , X and n are as defined for
 formula (I), R^{30} is H or alkyl and Y represents
 20 $C_{1-6}alkylidene$ with an amine of formula $HNR^aC_{1-6}alkylR^{12}$,
 $HNR^{13}C_{2-6}alkenyl$, $HNR^{13}C_{2-6}alkynyl$, $HNR^aC(NR^b)NR^cR^9$,
 $HNR^aheteroaryl$ or



in the presence of a base.

Suitable bases of use in the reaction include
 30 organic bases such as tertiary amines, for example,
 triethylamine.

The reaction is preferably effected in the presence of a coupling agent such as, for example, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

- 18 -

The reaction is conveniently effected in a suitable organic solvent, such as an ether, for example, tetrahydrofuran, suitably at ambient temperature.

Compounds of formula (I) may also be prepared
5 from different compounds of formula (I) by interconversion processes. In particular, interconversion processes may be used to vary the group R^8 .

Intermediates of formulae (II) and (III) may be
10 prepared as described in published European patent application no. 0 528 495.

Where the above-described process for the preparation of the compounds according to the invention gives rise to mixtures of stereoisomers these isomers
15 may, if desired, be separated, suitably by conventional techniques such as preparative chromatography.

The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. For example,
20 any suitable intermediates may be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric esters or amides, followed by chromatographic separation or separation by fractional crystallization and removal of the chiral auxiliary. The
25 diastereomeric intermediates can then be used to prepare optically pure compounds of formula (I).

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This
30 may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The

- 19 -

protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

- 20 -

DESCRIPTION 1

cis-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenyl
piperidine hydrochloride salt

5

a) A solution of methyl 4-nitrobutyrate (23g) and benzaldehyde (16ml) in acetic acid (39ml) containing ammonium acetate (12.12g) was heated at reflux under nitrogen for 2h. The reaction mixture was cooled to 5°C, whereby a pale-yellow solid
10 crystallised. This was isolated by filtration, then dissolved in dichloromethane, washed cautiously with saturated aqueous sodium bicarbonate solution (2 x), then dried (MgSO₄) and concentrated to leave a yellow solid. Recrystallisation from ethyl acetate provided 5-nitro-2-oxo-6-phenylpiperidine (12.5g) as a
15 crystalline, white solid. ¹H NMR (CDCl₃) δ 7.46-7.26 (m), 6.0 (br s), 5.24 (dd, J = 1.4, 7.0Hz), 4.70 (m), 2.70-2.50 (m), 2.38-2.24 (m).

b) Potassium *t*-butoxide (1.68g) was added to a solution of 5-nitro-2-oxo-6-phenylpiperidine (3g) in a mixture of dichloromethane
20 (50ml) and methanol (50ml) and the mixture was cooled to -78°C under nitrogen. Ozone was bubbled through the solution for 3h. A yellow-green solution resulted, and TLC indicated no starting material remained. The reaction mixture was purged with oxygen for 5 min to remove excess ozone, then dimethylsulfide (7ml) was added
25 and the reaction mixture was allowed to warm to 23°C. The solvent was removed *in vacuo*, and the residue was partitioned between dichloromethane and water. The layers were separated, and the aqueous phase was extracted twice with dichloromethane. The combined organic extracts were washed with brine, then dried
30 (K₂CO₃) and concentrated to leave a yellow solid.

This crude material was slurried in dry THF and added to lithium aluminium hydride (1M in THF, 50ml) then heated at

- 21 -

reflux for 12h. After cooling to 23°C, the reaction mixture was quenched by the cautious addition of water (dropwise) under nitrogen, then 2M sodium hydroxide. The mixture was filtered through a pad of Hyflo, the filtrate was washed with brine, then
5 dried (K_2CO_3) and concentrated to leave a yellow solid.

Purification by silica-gel chromatography ($CH_2Cl_2/MeOH/NH_3$ 97:3:1 then $CH_2Cl_2/MeOH$ 95:5) provided 3-hydroxy-2-phenylpiperidine as a ca 4:1 mixture of *cis*- and *trans*-isomers respectively. 1H NMR ($CDCl_3$) 7.44-7.20 (m), 3.84 (2), 3.76 (s),
10 3.54 (m), 3.4 (s), 3.3 (d, $J = 8Hz$), 3.26 (m), 3.04 (m) 2.78 (ddd, $J = 2.9, 11.9, 11.9Hz$), 2.70 (ddd, $J = 2.9, 11.9, 11.9Hz$), 2.18-1.78 (m), 1.48 (m). MS (EI) m/z 177 (M^+).

c) Di-*t*-butyldicarbonate (1.36g) was added to a solution of
15 3-hydroxy-2-phenylpiperidine (1g) in dichloromethane (8ml) under nitrogen and the mixture stirred at 23°C for 3h. The solvent was removed *in vacuo*, and the residue purified by silica-gel chromatography ($CH_2Cl_2/MeOH/NH_3$ 97:3:0.5) to provide *cis*- and *trans*-1-*t*-butyloxycarbonyl-3-hydroxy-2-phenylpiperidine (1.4g) as a
20 clear, viscous oil. 1H NMR ($CDCl_3$) δ 7.50-7.42 (m), 7.40-7.14 (m), 5.36 (d, $J = 5.6Hz$), 4.50 (m), 4.44 (m), 4.12-3.92 (m), 3.02 (ddd, $J = 3.0, 12.5, 12.5Hz$), 2.87 (ddd, $J = 3.0, 12.5, 12.5Hz$), 1.88-1.66 (m), 1.46 (s), 1.36 (s).

25 d) To a cooled (0°C) solution of 1-*t*-butyloxycarbonyl-3-hydroxy-2-phenylpiperidine (1.4g) in dry dimethylformamide (5ml) was added sodium hydride (80% dispersion in mineral oil; 182mg). The cooling bath was removed and the reaction mixture stirred at 23°C for 30 min. A solution of 3,5-bis(trifluoromethyl)
30 benzyl bromide (1.87g) in dry dimethylformamide (1ml) was added and stirring was continued for 2h at room temperature. The mixture was diluted with water (100ml) and extracted with ethyl acetate (3 x 40ml). The combined organic extracts were

- 22 -

washed with brine (1 x 30ml), dried (MgSO₄) and evaporated to yield a pale yellow oil. Purification by chromatography on silica using gradient elution of hexane in ethyl acetate (9:1 - 4:1) afforded the product cis-1-*t*-butyloxycarbonyl-3-((3,5-bis
5 (trifluoromethyl)phenyl)methoxy)-2-phenylpiperidine (350mg) as a clear viscous oil. ¹H NMR (250MHz, CDCl₃) δ 7.77 (1H, s, ArH), 7.71 (2H, s, ArH), 7.53-7.57 (2H, m, ArH), 7.2-7.4 (3H, m, ArH), 5.70 (1H, br d, app. J = 7.0Hz, NCHPh), 4.73 (2H, brs, OCH₂), 3.84-3.98 (2H, m, NCHCHO + NCHH), 2.77 (1H, ddd, J=13.0, 13.0, 3.0Hz), 2.00 (2H, mc, CH₂), 1.6-1.8 (2H, m, CH₂), 1.40 (9H, s, C(CH₃)₃).

e) Trifluoroacetic acid (3ml) was added to the product of (d) above (800mg) under nitrogen and the resulting solution was stirred for 1h. Excess trifluoroacetic acid was removed *in vacuo* and the residue was partitioned between 2M sodium hydroxide and dichloromethane. The organic phase was washed with brine, dried (MgSO₄) and evaporated to afford a colourless oil. Purification on silica (dichloromethane in methanol, 98:2 - 95:5) afforded the product cis-3-((3,5-bis(trifluoromethyl)phenyl)
15 methoxy-2-phenylpiperidine (360mg) as a colourless oil. ¹H NMR (360MHz, CDCl₃) δ 7.78 (1H, s, ArH), 7.44 (2H, s, ArH), 7.18-7.38 (5H, s, ArH), 4.52 (1H, d, J = 12.5Hz, OCHH), 4.13 (1H, d, J = 12.5Hz, OCHH), 3.84 (1H, d, J = 1.0Hz, NCHPh), 3.68 (1H, d, J = 1.5Hz), 3.28 (1H, m, NCHCHO), 2.84 (1H, ddd, J = 3.0, 12.5, 12.5Hz, NCHH), 2.20 (1H, mc, NCHH), 1.8-1.98 (2H, m, CH₂), 1.64-1.78 (1H, m, CHH), 1.50-1.58 (1H, m, CHH); MS m/z 404 ((M+1)⁺, 90%).

30 The oil was dissolved in ether to which was added excess ethereal hydrogen chloride. Upon standing a white solid crystallised. This was filtered and recrystallised from ethyl acetate-methanol to afford the title compound as white crystals:

- 23 -

mp 200-203°C. ¹H NMR (360MHz, DMSO) δ 7.95 (1H, s, ArH), 7.81 (2H, s, ArH), 7.37-7.47 (5H, m, ArH), 4.78 (1H, d, J = 13.0Hz, OCHH), 4.56 (1H, s, NCHPh), 4.32 (1H, d, J = 13.0Hz, OCHH), 3.96 (1H, s, NCHCHO), 3.10 (1H, t, J = 13.0Hz, NCHH), 2.23 (1H, d, J = 13.0Hz, NCHH), 1.64-2.00 (4H, m, CH₂ x 2); MS (CI⁺) m/z 404 ((M+1)⁺, 90%); Found: C, 54.08; H, 4.47; N, 3.13. Calcd. for C₂₀H₂₀F₆NOCl.0.25H₂O: C, 54.06; H, 4.65; N, 3.15%.

DESCRIPTION 2

(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-1-(carbomethoxy)methyl-2-phenylpiperidine

cis-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenyl piperidine hydrochloride (Description 1, 1g) was liberated from the hydrochloride salt by partitioning between ethyl acetate and 2M sodium hydroxide. The organic phase was washed successively with water, saturated brine, dried (MgSO₄) and evaporated *in vacuo*. To a solution of the residual oil in tetrahydrofuran (20ml) was added triethylamine (0.4ml) and methyl bromoacetate (400mg) and the solution was heated at reflux under an atmosphere of nitrogen for 16h. To the cooled solution was added ethyl acetate and water and the organic phase washed further with water and dried (MgSO₄). After the solvent had been removed *in vacuo* the residue was chromatographed on silica gel eluting with ethyl acetate/petroleum ether (3:10). The product was recrystallised from diethyl ether/petroleum ether to give the title compound, mp =81-83°C. Found: C, 57.35; H, 4.98; N, 2.84; C₂₃H₂₃F₆NO₃.0.1(H₂O) requires C, 57.71; H, 4.86; N, 2.93%. MS (CI⁺) m/z = 476 (M+H)⁺.

- 24 -

DESCRIPTION 3(+)-(2S,3S)-cis-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenylpiperidine hydrochloride salt

5

a) The mixture of *cis*- and *trans*-isomers of 3-hydroxy-2-phenylpiperidine (Description 1, (2b)) and 4-toluenesulfonic acid monohydrate was crystallized from methanol/ethyl acetate to give *cis*-3-hydroxy-2-phenylpiperidinium tosylate, mp 10 266-267°C.

b) The tosylate salt (Description 3(a) above) was dissolved in a mixture of ethyl acetate and 10% aqueous Na₂CO₃ with warming. The organic phase was washed with saturated brine, 15 dried (K₂CO₃) and evaporated to give crystalline *cis*-3-hydroxy-2-phenylpiperidine, mp 110-110.5°C.

c) *cis*-3-Hydroxy-2-phenylpiperidine (Description 3b) and (-)-dibenzoyltartrate were dissolved in methanol and crystallized 20 by addition of ethyl acetate. The solid was recrystallised from hot methanol to give the hemi dibenzoyltartrate salt, mp 223-224°C. This was liberated from the salt as described above to give the single enantiomer (+)-*cis*-3-hydroxy-2-phenylpiperidine, mp 93-95°C. $[\alpha]^{23}_D = +98.5^\circ$ (c=1, MeOH). 25 The mother liquors were converted to the free base as described in Description 3b and crystallization using (+)-dibenzoyltartrate in an analogous manner to that described above gave (-)-3-hydroxy-2-phenylpiperidine, mp 93-95°C. $[\alpha]^{23}_D = -97.2^\circ$ (c=1, MeOH).

30

d) (+)-*cis*-3-Hydroxy-2-phenylpiperidine was reacted according to the procedure detailed in Description 1c-e to give (+)-*cis*-3-((3,5-bis (trifluoromethyl)phenyl)methoxy)-2-

- 25 -

phenylpiperidine hydrochloride as a crystalline solid: mp
215-216°C. $[\alpha]_D = +87.3^\circ\text{C}$ (c=1, MeOH). ^1H NMR (360MHz,
DMSO- d_6) δ 7.95 (1H, s, ArH), 7.81 (1H, s, ArH), 7.47 (2H, m,
ArH), 7.37 (3H, m, ArH), 4.78 (1H, d, J = 13.0Hz, OCHH), 4.56
5 (1H, s, NCHPh), 4.32 (1H, d, J = 13.0Hz, OCHH), 3.96 (1H, s,
NCHCHO), 3.10 (1H, t, J = 13.0Hz, NCHH), 2.23 (1H, d, J =
13.0Hz, NCHH), 2.00-1.64 (4H, m, $\text{CH}_2 \times 2$); MS (CI^+) m/z 404
($\text{M}+1^+$, 90%); Found: C, 54.52; H, 4.60; N, 3.11. Calcd. for
 $\text{C}_{20}\text{H}_{19}\text{F}_6\text{NO} \cdot \text{HCl}$: C, 54.62; H, 4.58; N, 3.18%.

10

DESCRIPTION 4

(+)-(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-
1-(carbomethoxy)methyl-2-phenylpiperidine

15

The title compound was prepared from (+)-cis-3-((3,5-bis
(trifluoromethyl)phenyl)methyloxy)-2-phenylpiperidine
(Description 3) using the procedure detailed in Description 2:
mp 60-70°C. $[\alpha]_D = +132.3^\circ$ (c=1, MeOH). ^1H NMR (360MHz,
20 CDCl_3) δ 1.57-1.63 (3H, m, $\text{CH}_2 + \text{CHH}$), 2.04-2.17 (2H, m, CHH,
CHHN), 3.07-3.10 (1H, m, NCHCHO), 3.20 (1H, d, J = 17.0Hz,
NCHHCO $_2$ CH $_3$), 3.31 (1H, d, J = 17.0Hz, NCHCH CO $_2$ CH $_3$), 3.58
(3H, s, CH $_3$), 3.93 (1H, s, NCHPh), 4.07 (1H, d, J = 12.0Hz,
OCHH), 4.49 (1H, d, J = 12.0Hz, OCHH), 7.28-7.34 (3H, m,
25 ArH), 7.43-7.45 (2H, m, ArH), 7.54 (2H, s, ArH), 7.71 (1H, s,
ArH). MS (CI^+) m/z 476 ($\text{M}+1^+$, 100%). Found: C, 58.31; H,
4.90; N, 2.94. Calcd. for $\text{C}_{23}\text{H}_{23}\text{F}_6\text{NO}_3$: 58.11; H, 4.88; N, 2.95%.

30

DESCRIPTION 5

(2R*,3R*)-3-((3,5-Bis(trifluoromethyl) phenyl)methyloxy)-
1-(carboxymethyl)-2-phenylpiperidine.

- 26 -

The ester of Description 2 (4.98g) was dissolved in anhydrous THF (80ml) and an aqueous solution of potassium hydroxide (1.76g). The reaction was brought to reflux for 3 hrs and allowed to cool. The THF was removed *in vacuo* and the residue freeze dried, this afforded a yellow solid, which was dissolved in the minimum amount of water and the pH adjusted to 6.0 by careful addition of 1M HCl. A white precipitate was formed, this was filtered, re-dissolved in ethyl acetate and dried (MgSO₄). The solvent was removed *in vacuo* to afford a yellow solid (4.59g). The product was recrystallised from ethyl acetate/petrol as the zwitterion: mp 172-175°C. ¹H NMR (360MHz, DMSO) δ 1.44-1.60 (2H, m, CH₂), 1.82-1.97 (1H, m, CHH), 2.12-2.24 (1H, m, CHH), 2.46-2.63 (1H, m, CHH), 2.80 (1H, d, J = 17.0Hz, NCHH) 3.02-3.06 (1H, m, CHH) 3.12 (1H, d, J = 17.0Hz, NCHH), 3.57 (1H, s, CHO), 3.80 (1H, m, NCHPh), 4.09 (1H, d, J = 13Hz, OCHH), 4.63 (1H, d, J = 13Hz, OCHH), 7.22-7.40 (5H, m, Ar-H), 7.70 (2H, s, ArH), 7.93 (1H, s, ArH); MS(CI⁺) m/z 462 (M⁺+1, 30%); Found: C, 57.33 ; H, 4.59 ; N, 3.14. Calcd. for C₂₂ H₂₁ F₆ N O₃: C, 57.26 ; H, 4.59 ; N, 3.04.

DESCRIPTION 6

(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-1-(carboxymethyl)-2-phenylpiperidine

The title compound was prepared from the compound of Description 4 using the procedure detailed in Description 5: MS(CI⁺) m/z 462 (M⁺+1).

EXAMPLE 1

(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenyl-1-(N-(prop-2-ynyl)carboxamidomethyl)piperidine

The product of Description 5 (1g) was dissolved in anhydrous THF (40ml) under nitrogen. 1-Hydroxybenzotriazole

- 27 -

hydrate (1.2g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.66g), triethylamine (1.2ml) and propargylamine (0.55ml) were added and the reaction was allowed to stir overnight at room temperature. The solvent was removed *in vacuo* and the residual yellow oil dispersed between water and ethyl acetate. The organic layer was washed with 1M citric acid, water, sodium hydrogen carbonate, brine, dried (MgSO₄) and concentrated *in vacuo* to afford a yellow oil. This was purified on silica using 50% ethyl acetate in petrol as eluant. The product was purified further by medium pressure chromatography eluting with 30% ethyl acetate in petrol to afford the title compound as a colourless oil. ¹H NMR (360 MHz, DMSO) δ 1.54-1.68 (2H, m, CH₂), 2.00-2.34 (4H, m, NCH₂CH₂ + NHCH₂C=CH), 2.55 (1H, d, J = 16Hz, NCH₂CONH), 3.07 (1H, bd, NCH₂), 3.20 (1H, d, J = 16 Hz, NCH₂CONH), 3.45 (1H, m, CHO), 3.59 (1H, m, CHPh), 4.00-4.18 (3H, m, OCH₂ + NHCH₂CCH), 4.48 (1H, d, J = 12Hz, OCH₂), 7.13-7.40 (6H, m, ArH+NH), 7.55 (2H, s, ArH), 7.74 (H, s, ArH); MS (CI⁺) 497 (M+1⁺, 20%); Found: C, 59.81; H, 4.81; N, 5.54. Calcd. for C₂₅H₂₄N₂O₂F₆: C, 60.20; H, 4.85; N, 5.62%.

EXAMPLE 2

(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-1-(N-furfurylcarboxamidomethyl)-2-phenylpiperidine

Following the method of Example 1, the product of Description 5 was reacted with furfurylamine to afford the title compound: mp 80-83°C. Found: C, 59.83; H, 4.84; N, 5.32; Calcd. for C₂₇H₂₇F₆N₃O₃: C, 59.99; H, 4.85; N, 5.18%

EXAMPLE 3

(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-2-phenyl-1-(N-(3-pyridylmethyl)carboxamidomethyl)piperidine.

- 28 -

Following the method of Example 1, the product of Description 5 was reacted with 3-(aminomethyl) pyridine to give the title compound: mp 127-130°C. Found: C, 60.75; H, 5.05; N, 7.34; Calcd. for $C_{28}H_{27}F_6N_3O_2$: C, 60.98; H, 4.93; N, 7.62%

5

EXAMPLE 4

(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-1-(N-(2-methoxyethyl)carboxamidomethyl)-2-phenylpiperidinium hydrochloride

10

Following the method of Example 1, the product of Description 5 was reacted with 2-methoxyethylamine to give the title compound after treatment with ethereal HCl: mp 146-148°C. Found: C, 53.85; H, 5.37; N, 4.79; Calcd. for $C_{25}H_{28}F_6N_3O_3$ HCl: C, 54.11; H, 5.27; N, 5.05%.

15

EXAMPLE 5

(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-1-(carboxyhydrazidomethyl)-2-phenylpiperidinium hydrochloride

20

Hydrazine hydrate (3.0ml) was added to a solution of the compound of Description 2 (2.95g) in ethanol (80ml). The solution was heated to reflux for 18h after which the ethanol was removed *in vacuo*. The residue was extracted into ethyl acetate and the organic layer was washed with brine, dried ($MgSO_4$) and concentrated to give the title compound (2.79g). This was dissolved in methanol (5ml) and a methanolic solution of hydrogen chloride was added. Methanol was removed *in vacuo* and the salt was recrystallised from diethyl ether to give the hydrochloride salt. 1H NMR (360MHz, DMSO) δ 1.77-1.93 (2H, m, CH_2), 2.08-2.21 (1H, m, CH_2), 2.22-2.35 (1H, m, CH_2), 3.56 (1H, d, $NCHHCH_2$), 3.64 (1H, d, $J = 16.5Hz$, $NCHHCO$), 3.77 (1H, d, $NCHHCH_2$), 3.92 (1H, d, $J = 16.5Hz$, $NCHHCO$), 3.96 (1H, brs, CHO), 4.37 (1H, d, $J = 13.0Hz$, $OCHH$), 4.83 (1H, d, $J = 13.0Hz$, $OCHH$), 4.95 (1H, s, $CHPh$), 7.36-7.46 (3H, m, ArH),

30

- 29 -

7.53-7.62 (2H, brs, ArH), 7.95 (2H, s, ArH), 7.97 (1H, s, ArH);
MS (CI)⁺ m/z 475.

EXAMPLE 6

5 (2S,3S)-1-(N-Amidino(carboxamidomethyl))-3-((3,5-bis
 (trifluoromethyl)phenyl)methoxy-2-phenylpiperidine

 Guanidine hydrochloride (600mg) was added to a solution of
sodium (150mg) in methanol (30ml) and the solution was heated at
reflux for 30 min. To this solution was added the ester of
10 Description 4 and the resulting solution was heated at reflux for 1h.
 The solution was cooled, and concentrated *in vacuo*. The residue
 was dispersed between ethyl acetate and water. The organic phase
 was separated, dried (MgSO₄) and concentrated. The residue was
 purified by chromatography on alumina (grade III) using a gradient
15 elution of 1-10% methanol in dichloromethane. This afforded the
 desired product which was recrystallised from ether/hexane: mp
 159-160°C. Found: C, 54.77; H, 4.99; N, 11.19. Calcd. for
 C₂₃H₂₄F₆N₄O₂: C, 54.98; H, 4.81; N, 11.15%.

20

EXAMPLE 7

(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-
 phenyl-1-(N-methyl-N-(3-pyridylmethyl)carboxamidomethyl)
 piperidinium hydrobromide

 (a) (N-(Chloroacetyl)-N-methylaminomethyl)pyridinium
25 hydrochloride

 Chloroacetyl chloride (790mg) was added dropwise to a
chilled solution of 3-(N-methylaminomethyl)pyridine in
dichloromethane (30ml). The resulting solution was stirred at
30 5°C for 2h. Removal of solvent afforded the product as a white
 crystalline solid: mp 120-121°C. ¹H (360MHz DMSO-d₆) 3.1
 (3H, s, NMe), 4.50 (2H, s, ClCH₂CO), 4.75 (2H, s,

- 30 -

N-CH₂-pyridine), 8.01 (1H, dd, J=6.0, 5.5Hz, ArH), 8.43 (1H, m, ArH), 8.89 (2H, m, ArH); MS m/z (CI⁺) 199 (M⁺+1).

5 (b) (2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-
2-phenyl-1-(N-methyl-N-(3-pyridylmethyl)carboxamidomethyl)
piperidine dihydrobromide

Diisopropylethylamine (4.3ml) was added to a stirred
suspension of 3-(N-(chloroacetyl)-N-methylaminomethyl)pyridine
10 hydrochloride (1.6g) and the compound of Description 3 (3.6g).
The resulting solution was stirred at room temperature for 18h.
After this time the white precipitate was filtered off and the
solvent removed under reduced pressure. The solid residue was
taken up in water (50ml) and extracted into ethyl acetate
15 (2x50ml). The organic extracts were combined, dried (MgSO₄),
filtered and the solvent removed under reduced pressure. The
product was isolated by flash chromatography on silica gel using
20% ethyl acetate in hexane as eluent. The isolated free base
was treated with a solution of hydrogen bromide in ether,
20 followed by recrystallisation from methyl-*t*-butyl ether to afford
the product as an amorphous solid: mp 68-70°C. ¹H NMR
(360MHz, CDCl₃, free base), 1.6 (2H, m, CH₂CH₂N), 2.1 (2H, m,
CH₂CH₂), 2.68 (3H, s, NCH₃), 2.79 (2H, s, CH₃N-CH₂), 3.15 (2H,
m, CH₂ NCH), 3.59 (1H, bs, NCH-Ph), 4.08 (2H, m, CH-O-CH₂Ar
25 and CHH-CO), 4.3 (1H, d, J=10.0Hz, OCHH-Ar), 4.60 (2H, m,
CHHCO and OCHH-Ar), 7.1-7.25 (7H, m, Ar-H), 7.51 (2H, s,
ArH), 7.63 (1H, s, ArH), 8.15-8.3 (2H, m, Ar-H): MS m/z (CI⁺)
567 (M⁺+1). Found: C, 46.63; H, 4.64; N, 5.46. Calcd. for
C₂₉H₂₉F₆N₃O₂ · 2HBr·H₂O: C, 46.72; H, 4.46; N, 5.63%.

- 31 -

EXAMPLE 8(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-1-(2-morpholino-2-oxo)ethyl-2-phenylpiperidinium hydrochloride

5

The compound of Description 6 (2g), triethylamine (2.42ml), morpholine (1.5ml), hydroxybenzotriazole (2.35g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.66g) were suspended in dimethylformamide (25ml) and the reaction mixture was allowed to stir under nitrogen for 12h. The solvent was removed *in vacuo* and the residual yellow oil was dispersed between water and ethyl acetate. The organic layer was washed successively with 1M citric acid, water, sodium hydrogen carbonate solution, brine, then dried (MgSO₄) and concentrated *in vacuo* to afford a yellow oil. This was purified by chromatography on silica using 70% ethyl acetate in petrol as eluent. This afforded the title compound as a colourless oil. Treatment of this oil with ethereal hydrogen chloride afforded the hydrochloride salt which was recrystallised from ethyl acetate/petrol: mp 90-91°C. ¹H NMR (360MHz, DMSO-d₆) δ 1.49-1.52 (2H, m, CH₂), 1.89-1.90 (1H, m, CH₂), 2.12-2.18 (1H, m, CH₂), 2.41-2.47 (1H, m, CH₂N), 2.76 (1H, d, J=15.0Hz, NCH₂HCO), 2.96-2.99 (1H, m, CH₂N), 3.16 (1H, d, J=15.0Hz, NCH₂HCO), 3.29-3.32 (2H, m, CH₂-morpholine), 3.43-3.48 (6H, m, CH₂-morpholine), 3.57 (1H, s, CHO), 3.61 (1H, s, NCH₂Ph), 4.15 (1H, d, J=13.0Hz, OCH₂H), 4.65 (1H, d, J=13.0Hz, OCH₂H), 7.24-7.28 (3H, m, ArH), 7.39-7.41 (2H, m, ArH), 7.76 (2H, s, ArH), 7.94 (1H, s, ArH); MS (CI⁺) m/z 530 (M+1)⁺, 70%. Found: C, 53.82; H, 5.35; N, 4.90; Cl, 6.20; Calcd. for C₂₆H₂₈F₆N₂O₃.HCl.H₂O: C, 53.38; H, 5.34; N, 4.79; Cl, 6.06%.

30

- 32 -

EXAMPLE 9

(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-1-(2-oxo-2-piperidino)ethyl-2-phenylpiperidinium hydrochloride

5

The title compound was prepared following the method described in Example 8, using piperidine as a starting material; this afforded a white crystalline material: mp 89-91°C. ¹H NMR (360MHz, DMSO-d₆) δ 0.85-0.92 (1H, m, CHH), 1.08-1.14 (1H, m, CHH), 1.25-1.34 (2H, m, CH₂), 1.38-1.46 (2H, m, CH₂), 1.76-1.88 (2H, m, CH₂), 2.20-2.32 (2H, m, CH₂), 2.49-2.51 (4H, m, 2xCH₂), 3.16-3.24 (1H, m, CHHN), 3.40-3.48 (1H, m, CHHN), 3.82 (1H, d, J=17.0Hz, N-CHHCO), 3.93 (1H, d, J=17.0Hz, N-CHHCO), 3.98 (1H, s, CHO), 4.43 (1H, d, J=13.0Hz, OCHH), 4.86 (1H, d, J=13.0Hz, OCHH), 5.07 (1H, s, NCHPh), 7.24-7.27 (3H, m, ArH), 7.41-7.44 (2H, m, ArH), 7.80 (2H, s, ArH), 7.95 (1H, s, ArH); MS (CI⁺) m/z 529 ((M+1)⁺, 100%).

10
15EXAMPLE 10

20

(2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-1-(2-oxo-2-(4-methylpiperazinyl))ethyl-2-phenylpiperidinium hydrochloride

25

The title compound was prepared following the method described in Example 8 using N-methylpiperazine as a starting material; this afforded the product as a white powder. ¹H NMR (360MHz, DMSO-d₆) δ 1.48-1.52 (2H, m, CH₂), 1.8-1.90 (1H, m, CHH), 2.18-2.24 (1H, m, CH₂), 2.38-2.44 (1H, m, NCHH), 2.50 (3H, s, CH₃), 2.71 (1H, d, J=14.0Hz, CHHCO), 2.94-2.97 (1H, m, NCHH), 3.15 (1H, d, J=14.0Hz, CHHCO), 3.20-3.25 (2H, m, CHO), 3.25-3.31 (4H, m, NCH₂CH₂N), 3.42-3.57 (4H, m, NCH₂CH₂N), 4.15 (1H, d, J=13.0Hz, OCHH), 4.65 (1H, d,

30

- 33 -

$J=13.0\text{Hz}$, OCHH), 7.24-7.26 (3H, m, ArH), 7.39-7.42 (2H, m, ArH), 7.76 (2H, s, ArH), 7.95 (1H, s, ArH); MS (Cl^+) m/z 543 ($(\text{M}+1)^+$, 80%).

5

EXAMPLE 11

(2R*, 3R*)-3-Benzoyloxy-1-(2-morpholino-2-oxo)ethyl-2-phenylpiperidinium hydrochloride

10

(a) Bromoacetylmorpholine

15

Bromoacetyl bromide (20.1g) was added dropwise to a rapidly stirred solution of morpholine (17.4g) in ether (200ml). After stirring overnight, the mixture was washed with water (2 x 50ml), dried (MgSO_4) and evaporated to afford a colourless oil. ^1H NMR (360MHz, CDCl_3) δ 3.46 (2H, m, 2 x CHHN), 3.63 (2H, m, 2 x CHHN), 3.69 (4H, m, 2 x CH_2O), 3.75 (2H, s, CH_2Br).

20

(2R*, 3R*)-3-Benzoyloxy-1-(2-morpholino-2-oxo)ethyl-2-phenylpiperidinium hydrochloride

25

A mixture of the compound of Description 1 (139mg), bromoacetylmorpholine (208mg) and potassium carbonate (50mg) in dimethylformamide (10ml) was heated to 100°C under N_2 for 5h. The mixture was cooled, diluted with water (50ml) and extracted with ethyl acetate (2 x 50ml). The combined extracts were washed with brine (50ml), dried (MgSO_4) and evaporated to afford a yellow oil. This was purified by column chromatography on silica eluting with ethyl acetate to afford a colourless oil. Formation of the hydrochloride salt and recrystallisation from ethyl acetate/hexane afforded the title compound; mp $84-85^\circ\text{C}$.

30

- 34 -

EXAMPLE 12(2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenyl-1-(thiocarboxamidomethyl)piperidine

5

(a) (2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-1-(cyanomethyl)-2-phenylpiperidinium hydrochloride

10 The compound of Description 1 (5g), potassium carbonate (1.7g) and bromoacetonitrile (0.87ml) were suspended in dimethylformamide (15ml) and the mixture was stirred under nitrogen at 60°C for 3h. The mixture was cooled, diluted with water (200ml) and extracted with ethyl acetate (2 x 50ml). The organic extracts were washed with brine, dried (MgSO₄) and

15 evaporated, affording a brown oil. This was purified on silica using ethyl acetate in petrol (10%) as eluant. This afforded the product as a colourless oil. The hydrochloride salt was prepared by dissolution in ethereal hydrogen chloride and the salt was recrystallised from ether-hexane: mp 133-134°C. ¹H NMR

20 (360MHz, CDCl₃) δ 1.75 (2H, mc, CH₂), 1.90 (2H, mc, CH₂), 2.31 (1H, mc, CH₂), 2.71 (1H, mc, CH₂), 3.19 (1H, mc, CH₂N), 3.72 (1H, mc, CH₂N), 3.81 (1H, d, J = 17.5Hz, NCH₂HCN), 3.86 (1H, s, CHO), 4.02 (1H, d, J = 17.5Hz, NCH₂HCN), 4.09 (1H, s, CHPh), 4.35 (1H, d, J = 13.0Hz, OCH₂), 4.73 (1H, d, J = 13.0Hz, OCH₂),

25 7.4 (3H, mc, ArH), 7.69-7.73 (5H, m, ArH); MS (CI⁺) m/z 443 (M⁺+1, 30%). Found: C, 54.87; H, 4.30; N, 5.66. Calcd. for C₂₂H₁₈F₆N₂O.HCl: C, 55.18; H, 4.42; N, 5.85%.

30 (b) (2R*,3R*)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenyl-1-(thiocarboxamidomethyl)piperidine

The compound of (b) above (1g) was dissolved in dimethylformamide (anhydrous, 10ml) and the solution was

- 35 -

saturated with dry hydrogen chloride gas. The reaction was heated to 100°C under nitrogen and thioacetamide (0.34g) was added; this mixture was allowed to stir at 100°C for 3h.

Dimethylformamide was removed *in vacuo*. The residue was extracted with ethyl acetate and the organic layer was washed with aqueous sodium bicarbonate, brine, dried (MgSO₄) and concentrated *in vacuo* to afford a brown oil. This was purified on silica using a gradient elution of ethyl acetate in petrol (10-50%). The product was further purified by recrystallisation from ethyl acetate-petrol; mp 164-166°C. ¹H NMR (360MHz, CDCl₃) δ 1.56-1.70 (2H, m, CH₂), 1.96-2.10 (1H, m, CHH), 2.15-2.32 (2H, m, CHHN + CHH), 2.98-3.06 (1H, bd, NCHH), 3.09 (1H, d, J = 18.0Hz, CHHSNH₂), 3.50 (1H, d, J = 18.0Hz, NCHHCSNH₂), 3.50 (1H, s, CHO), 3.60 (1H, s, NCHPh), 4.04 (1H, d, J = 12.0Hz, OCHHAr), 4.47 (1H, d, J = 12.0Hz, OCHHAr), 7.26-7.36 (5H, m, CHPh), 7.53 (2H, s, Ar-H), 7.75 (H, s, Ar-H), 7.61 (1H, bs, NHH), 8.99 (1H, bs, NHH); MS (CI⁺) m/z 477 (M⁺+1, 15%); Found: C, 55.09; H, 4.58; N, 5.97. Calcd. for C₂₂H₂₂F₆N₂OS: C, 55.46; H, 4.65; N, 5.88.

EXAMPLE 13

(2S, 3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-2-phenyl-1-(N-(2-pyridylmethyl)carboxamidomethyl)piperidine

The compound of Description 6 was reacted with 2-(aminomethyl)pyridine to afford the title compound: mp 112-114°C. Found: C, 61.27; H, 5.12; N, 7.59. Calcd. for C₂₈H₂₇F₆N₃O₂: C, 60.98; H, 4.93; N, 7.62%. MS (CI⁺) m/z 552 (M⁺ +1, 30%).

- 36 -

EXAMPLE 14

2-[(2S, 3S)-3-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-
2-(diphenylmethyl)pyrrolidinol-N-(carbomethoxy)acetamidrazone

5

(a) N-Carbomethoxy-2-chloroacetamidrazone

Sodium methoxide (0.032g) was added to a solution of
chloroacetonitrile (1.26ml) in anhydrous methanol (15ml) at 0°C.
10 The reaction mixture was stirred at room temperature for 0.5h
and then neutralised with acetic acid (0.034ml). Methyl
hydrazinocarboxylate (1.79g) was added and the reaction
mixture stirred at room temperature for 0.5h. The solution was
concentrated *in vacuo* to give the title compound as a white solid;
15 mp 138-140°C. MS (CI)⁺ m/z 166.

(b) (2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)
methoxy)-2-(diphenylmethyl)pyrrolidinium hydrochloride

20

(i) N-t-Butyloxycarbonyl-(S)-diphenylalanol

A solution of methyl sulfoxide (4.4ml) in dichloromethane
(13ml) was added dropwise to a cooled (-78°C) solution of oxalyl
chloride (4ml) in dichloromethane (50ml). After 15 min, a solution
of N-t-butyloxycarbonyl-(S)-diphenylalanol (10g) in dichloromethane
25 (150ml) was added dropwise at -30°C. The solution was allowed to
stir for 30 min, triethylamine (17ml) was added and the solution
was allowed to warm to -10°C. Ice-water (200ml) was added to the
solution which was then poured onto hexane (600ml). The organic
phase was separated, washed successively with citric acid (200ml),
30 saturated aqueous sodium bicarbonate (2 x 150ml), brine (1 x
150ml) then dried (MgSO₄) and concentrated *in vacuo* to leave a
white crystalline solid. ¹H NMR (250MHz, CDCl₃) δ 1.42 (9H, s,

- 37 -

C(CH₃)₃), 4.48 (1H, d), 4.86 (1H, d), 5.10 (1H, t), 7.26 (10H, m, ArH), 9.6 (1H, s, CHO).

5 (ii) N-*t*-Butyloxycarbonyl-1-(diphenylmethyl)-2-hydroxy-pent-4-enyl-1-amine

A solution of N-*t*-butyloxycarbonyl-(S)-diphenylalanal (10.9g) in tetrahydrofuran (60ml) was added dropwise to a solution of allyl magnesium chloride (2M in tetrahydrofuran, 36ml) at -10°C. After 30 min the mixture was poured onto
10 ice-cold saturated aqueous ammonium chloride and the resulting mixture was extracted with ethyl acetate (3 x 150ml). The combined organic extracts were washed with brine (1 x 100ml), then dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel using hexane in ethyl
15 acetate (gradient elution of 9:1 to 4:1) as eluant to afford the compound as a white solid. ¹H NMR (360MHz, CDCl₃) δ 1.42 (9H, s, (CH₃)₃), 2.22 (2H, m), 2.68 (3H, brs), 3.48 (t), 3.57 (1H, m), 3.86 (1H, s), 4.07 (d, J = 11Hz), 5.04 (1H, m), 5.71 (1H, m), 6.97-7.36 (10H, m, ArH).

20

(iii) 2-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-N-*t*-butyloxycarbonyl-1-(diphenylmethyl)-pent-4-enyl-1-amine

Sodium hydride (80% in oil, 0.53g) was added to a solution of 3,5-bis(trifluoromethyl)benzyl bromide (5ml) and the
25 compound of (13b) above (5g) in dimethylformamide (8ml). After stirring for 1h water (80ml) was added and the mixture was extracted with ethyl acetate (3 x 100ml). The combined organic extracts were washed with brine (1 x 100ml) then dried (MgSO₄) and concentrated to leave an oil which was purified on silica
30 using hexane in ethyl acetate as eluant (gradient elution of 97:3 to 4:1). This afforded the title compound as a colourless oil. ¹H NMR (360MHz, CDCl₃) δ 1.25 (s), 1.30 (s), 2.35 (m), 3.31 (m),

- 38 -

3.40 (dd, J = 5.2, 8.3Hz), 3.97 (d), 4.27 (d), 4.38 (m), 4.65 (m),
4.85 (d), 5.16-5.02 (m), 5.77 (m), 7.35-7.13 (m), 7.76 (s), 7.85 (s).

5 (iv) (2S,3S)-3-((3,5-Bis(trifluoromethyl)phenyl)
methoxy-2-(diphenylmethyl)pyrrolidinium hydrochloride

 A solution of the compound of (c) above (5.2g) in
dichloromethane (40ml) and methanol (40ml) was treated with a
stream of ozone in oxygen at -78°C for 1h. Methyl sulfide (3ml)
was added and the mixture was warmed to 23°C and concentrated
10 *in vacuo*. The residue was dissolved in chloroform (50ml),
triethylsilane (5.6ml) was added followed by dropwise addition of
a solution of trifluoroacetic acid (6.9ml) in chloroform (5ml). After
1h the solvent was evaporated *in vacuo* and trifluoroacetic acid
(10ml) was added to the residue. After stirring for 30 min the
15 mixture was concentrated *in vacuo* and the residue was
partitioned between dichloromethane and saturated aqueous
sodium bicarbonate. The organic layer was dried (K₂CO₃) and
concentrated to leave a brown oil. This was purified on silica gel
eluting with dichloromethane/methanol (99:1) to provide the title
20 compound as the free base. This was converted to the salt by
treatment with methanolic hydrogen chloride: mp >230°C. [α]²³_D
= +46.6°C (c=1, CH₃OH). Found: C, 59.95; H, 4.74; N, 2.63%.
Calcd. for C₂₆H₂₃F₆NO.HCl.0.2H₂O: C, 60.11; H, 4.73; N, 2.70%.

25 (c) The compound of (b) above (155mg) was stirred with
N-carbomethoxy-2-chloroacetamidrazone (a) (0.3g) in
dimethylformamide (5ml) in the presence of potassium carbonate
(260mg) at 70°C for 14h. After cooling, the material was
partitioned between ethyl acetate and water. The organic layer
30 was washed with brine, dried (MgSO₄) and filtered. The solvent
was evaporated and the residue was purified by chromatography
on silica using 5% methanol in ethyl acetate as eluant. ¹H NMR
(360MHz, CDCl₃) δ 1.93 (2H, m), 2.60 (1H, m), 2.68 (1H, d,

- 39 -

J=14Hz), 2.96 (1H, d, J=14Hz), 3.16 (1H, m), 3.70 (1H, m), 3.74 (3H, s), 4.09 (1H, m), 4.28 (2H, m), 4.66 (1H, brs), 7.35-7.11 (10H, m), 7.52 (2H, s), 7.77 (1H, s).

5

EXAMPLE 15

(2S, 3S)-3-(3,5-Bis(trifluoromethyl)phenyl)methoxy-1-bis(carbomethoxy)methyl-2-phenylpiperidine

10

The compound of Description 3 (0.439g) was dissolved in dimethylformamide (3ml) and dimethyl bromomalonate (0.274g) and potassium carbonate were added. The mixture was heated at 60°C overnight. The mixture was diluted with water and extracted into ethyl acetate. The organic phase was washed with

15

water, dried (MgSO₄) and evaporated. The residue was purified by chromatography on silica using gradient elution of 5-20% ethyl acetate in hexane. This afforded the product as a clear oil.

20

¹H NMR (360MHz, CDCl₃) δ 1.55-1.61 (2H, m), 2.04-2.17 (2H, m), 2.68-2.74 (1H, m), 3.37-3.41 (1H, m), 3.53 (1H, brs), 3.67 (3H, s, CH₃), 3.71 (3H, s, CH₃), 3.97 (1H, d, J=2Hz), 4.02 (1H, d, J=12.5Hz, OCHH), 4.26 (1H, s), 4.44 (1H, d, J=12.5Hz, OCHH), 7.25-7.34 (3H, m, ArH), 7.40-7.42 (2H, m, ArH), 7.51 (2H, s, ArH), 7.71 (1H, s, ArH).

25

EXAMPLE 16

(2S, 3S)-3-(3,5-Bis(trifluoromethyl)phenyl)methoxy-1-bis(carboxamido)methyl-2-phenylpiperidinium hydrochloride

30

(a) 2-Bromomalonamide

2-Cyanoacetamide (5g) was dissolved in glacial acetic acid (50ml) and stirred under nitrogen. Bromine (9.5g) was dissolved

- 40 -

in acetic acid and added dropwise to the solution; after 2h the mixture was evaporated to afford a white slurry. The title compound was recrystallised from ethanol. MS (CI⁺) m/z 181 (M+1⁺, 20%).

5

(b) (2S, 3S)-3-(3,5-Bis(trifluoromethyl)phenyl)methoxy)-1-bis(carboxamido)methyl-2-phenylpiperidinium hydrochloride

The compound of Description 3 (0.65g) was dissolved in dimethylformamide (5ml) under nitrogen and potassium carbonate (0.199g) and 2-bromomalonamide (0.35g) were added. The reaction mixture was stirred at 60°C for 3h. The compound was isolated following the procedure described in Example 15 and was purified by chromatography on silica using 4% methanol in dichloromethane as eluant to afford a white solid.

Treatment with ethereal hydrogen chloride afforded the title compound: mp 189-194°C. ¹H NMR (360MHz, CDCl₃) δ 1.56-1.74 (2H, m, NCH₂CH₂CH₂), 1.94-2.10 (1H, m, NCH₂CH₂), 2.15-2.24 (1H, m, NCH₂CH₂), 2.75-2.86 (1H, m, NCH₂CH₂), 2.97-3.07 (1H, m, NCH₂CH₂), 3.60 (H, bs, CHO, 3.85 (1H, bs, NCHPh), 4.13 (1H, d, J=12Hz, OCH₂Ar), 4.50-4.60 (2H, m, NCH(CONH₂)₂ + OCH₂Ar), 5.44 (1H, bs, NH), 5.71 (1H, bs, NH), 7.27-7.37 (3H, m, ArH), 4.43-7.50 (2H, m, ArH), 7.62 (2H, s, ortho H's), 7.76 (1H, s, para H's), 8.01-8.25 (2H, m, NH+NH). MS (CI⁺) m/z 504 (M+1⁺, 30%). C₂₃H₂₃N₃O₃F₆. HCl. requires C, 51.17; H, 4.48; N, 7.78. Found: C, 51.00; H, 4.27; N, 7.67.

EXAMPLE 17

(2S, 3S)-3-(3,5-Bis(trifluoromethyl)phenyl)methyloxy)-1-(N-methanesulfonyl)carboxamidomethyl)-2-phenylpiperidine

5 (a) N-Bromoacetylmethanesulfonamide

Sodium hydride (1.68g x 60%) was added to a stirred solution of methanesulfonamide (2.0g) in dry tetrahydrofuran (20ml) at room temperature. The resulting solution was stirred at room temperature for 1h, at which time it was treated with a solution of bromoacetyl bromide (4.2g) in dry tetrahydrofuran (10ml). After 1h the solvent was removed under reduced pressure and the residue taken up in water and acidified to pH3. The acidic solution was extracted into ethyl acetate, dried (MgSO₄), filtered and the solvent removed under reduced pressure. Recrystallisation from isopropanol afforded the product as white needles: mp 112-114°C.

(b) (2S, 3S)-3-(3,5-Bis(trifluoromethyl)phenyl)methyloxy)-1-(N-methanesulfonyl)carboxamidomethyl)-2-phenylpiperidine

Diisopropylethylamine (187mg) was added to a stirred solution of N-bromoacetylmethanesulfonamide (42mg) and the compound of Description 3 (300mg) in dry acetonitrile (10ml). The resulting solution was stirred for 18h at room temperature. Solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The organic layers were separated, dried (MgSO₄), filtered and the solvent removed under reduced pressure. Recrystallisation from ether/hexane afforded the product as a white powder: mp 127-130°C. C₂₃H₂₄N₂O₄F₆ · 0.25H₂O requires C, 50.87; H, 4.55; N, 5.16. Found: C, 50.73; H, 4.38; N, 5.07%.

- 42 -

The following examples illustrate pharmaceutical compositions according to the invention.

EXAMPLE 18A Tablets containing 1-25mg of compound

5		<u>Amount mg</u>		
	Compound of formula (I)	1.0	2.0	25.0
	Microcrystalline cellulose	20.0	20.0	20.0
	Modified food corn starch	20.0	20.0	20.0
	Lactose	58.5	57.5	34.5
10	Magnesium Stearate	0.5	0.5	0.5

EXAMPLE 18B Tablets containing 26-100mg of compound

		<u>Amount mg</u>		
	Compound of formula (I)	26.0	50.0	100.0
15	Microcrystalline cellulose	80.0	80.0	80.0
	Modified food corn starch	80.0	80.0	80.0
	Lactose	213.5	189.5	139.5
	Magnesium Stearate	0.5	0.5	0.5
20	The compound of formula (I), cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing			
25	1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active compound per tablet.			

EXAMPLE 19 Parenteral injection

		<u>Amount mg</u>
30	Compound of formula (I)	1 to 100mg
	Citric Acid Monohydrate	0.75mg
	Sodium Phosphate	4.5mg
	Sodium Chloride	9mg
	Water for Injections	to 1ml

- 43 -

The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The compound of formula (I) is dissolved or suspended in the solution and made up to volume.

5

EXAMPLE 20 Topical formulation

	<u>Amount mg</u>
Compound of formula (I)	1-10g
Emulsifying Wax	30g
10 Liquid paraffin	20g
White Soft Paraffin	to 100g

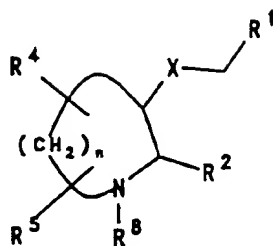
The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The compound of formula (I) is added and stirring continued until dispersed. The mixture is then cooled until solid.

15

- 44 -

CLAIMS:

1. A compound of formula (I), or a salt of
5 prodrug thereof:



(I)

15 wherein

n is 1, 2 or 3;

X represents O or S;

R¹ represents phenyl optionally substituted by
1, 2 or 3 groups selected from C₁-6alkyl, C₂-6 alkenyl,
20 C₂-6alkynyl, halo, cyano, nitro, trifluoromethyl,
trimethylsilyl, -OR^a, SR^a, SO₂R^a, -NR^aR^b, -NR^aCOR^b,
-NR^aCO₂R^b, -CO₂R^a and -CONR^aR^b;

R² represents aryl selected from phenyl and
naphthyl; heteroaryl selected from indazolyl, thienyl,
25 furyl, pyridyl, thiazolyl, tetrazolyl and quinolyl;
benzhydryl; or benzyl; wherein each aryl or heteroaryl
moiety may be substituted by C₁-6alkyl, C₁-6alkoxy, halo
or trifluoromethyl;

R⁴ and R⁵ may be present on any available
30 carbon atom of the azacyclic ring and each independently
represent H, halo, C₁-6alkyl, oxo, CH₂OR^a, CO₂R^a or
CONR^aR^b;

R⁸ represents C(COOR^a)₂, C(CONR^aR^b)₂ or
C₁-6alkyl substituted by C(=NR^a)NR^bNR^cCO₂R^d, CONHNR^aR^b,

- 45 -

$C(S)NR^aR^b$, $CONR^aC_{1-6}alkylR^{12}$, $CONR^{13}C_{2-6}alkynyl$,
 $CONR^{13}C_{2-6}alkenyl$, $COCONR^aR^b$, $CONR^aC(NR^b)NR^cR^d$,
 $CONR^{13}SO_2R^a$, $SO_2NR^{13}COR^a$, $CONR^aheteroaryl$ or COR^q ;

R^a , R^b , R^c and R^d each independently represent

5 H, $C_{1-6}alkyl$, phenyl or trifluoromethyl.

R^{12} represents OR^a , $CONR^aR^b$ or heteroaryl;

R^{13} represents H or $C_{1-6}alkyl$; and

R^q represents a group



15 where Q represents the residue of a non-aromatic
 azacyclic or azabicyclic ring system.

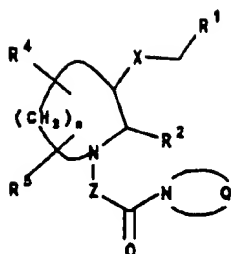
2. A compound as claimed in claim 1 wherein
 R^4 and R^5 each independently represent H, halo, $C_{1-6}alkyl$, oxo, CO_2R^{10} or $CONR^{10}R^{11}$; R^8 represents $C_{1-6}alkyl$
 20 substituted by a group selected from $CONHNR^aR^b$,
 $C(S)NR^aR^b$, $CONR^aC_{1-6}alkylR^{12}$, $CONR^{13}C_{2-6}alkynyl$,
 $CONR^{13}C_{2-6}alkenyl$, $COCONR^aR^b$, $CONR^aC(NR^b)NR^aR^b$, and
 $CONR^aheteroaryl$; or a salt or prodrug thereof.

25

3. A compound as claimed in claim 1 of
 formula (Ia):

30

- 46 -



(Ia)

10 wherein n , X , R^1 and R^2 are as defined for formula (I);
 Q is the residue of an azacyclic or a bridged azabicyclic
 ring system;

Z represents an alkyl chain of 1, 2, 3, 4, 5 or
 6 carbon atoms; and

15 R^4 and R^5 each independently represent H, halo,
 C_{1-6} alkyl, oxo, CO_2R^a or $CONR^aR^b$; or a salt or prodrug
 thereof.

4. A compound as claimed in claim 1 wherein
 20 R^8 represents $C(COO(C_{1-6}alkyl))_2$, $C(CONH_2)_2$ or $C_{1-6}alkyl$
 substituted by $C(=NH)NHNHCO_2C_{1-6}alkyl$, $CONHNH_2$, $COCONH_2$,
 $CONHC(NH)NH_2$, $CSNH_2$, $CONR^{13}C_{2-6}alkynyl$,
 $COR^9C_{1-6}alkylC_{1-6}alkoxy$, $CONHSO_2C_{1-6}alkyl$,
 $CONR^aC_{1-6}alkylheteroaryl$, $CONR^aheteroaryl$ or COR^q .

25 5. A compound as claimed in any preceding
 claim wherein n is 3.

6. A compound as claimed in any preceding
 30 claim wherein X is O.

7. A compound as claimed in any preceding
 claim wherein R^1 represents phenyl substituted by 1, 2 or

- 47 -

3 groups selected from C₁₋₄alkyl, trifluoromethyl and halo.

8. A compound as claimed in any preceding
5 claim wherein R² represents benzhydryl or phenyl optionally substituted by halo.

9. A compound as claimed in claim 1 selected
from
10 (2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-
2-phenyl-1-(N-(prop-2-ynyl)carboxamidomethyl)piperidine;
(2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-
1-(N-furfuryl)carboxamidomethyl)-2-phenylpiperidine;
15 (2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-
2-phenyl-1-(N-(3-pyridylmethyl)carboxamidomethyl)
piperidine;
(2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-
1-(N-(2-methoxyethyl)carboxamidomethyl)-2-phenyl
piperidine;
20 (2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-
1-(carboxyhydrazidomethyl)-2-phenylpiperidine;
(2S,3S)-1-(N-amidino(carboxamidomethyl))-3-((3,5-
bis(trifluoromethyl)phenyl)methyloxy)-2-phenylpiperidine;
(2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-2-
25 phenyl-1-[N-methyl-N-((3-pyridylmethyl)
carboxamidomethyl)]piperidine;
(2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-1-
(2-morpholino-2-oxo)ethyl-2-phenylpiperidine;
(2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-1-
30 (2-oxo-2-piperidino)ethyl-2-phenylpiperidine;
(2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-1-
(2-oxo-2-(4-methylpiperazinyl))ethyl-2-phenylpiperidine;
(2R*,3R*)-3-benzyloxy-1-(2-morpholino-2-oxo)ethyl-2-
phenylpiperidine;

- 48 -

- (2R*,3R*)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-
2-phenyl-1-(thiocarboxamidomethyl)piperidine;
(2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-2-
phenyl-1-(N-(2-pyridylmethyl)carboxamidomethyl)
5 piperidine;
2-[(2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-
2-(diphenylmethyl)pyrrolidino]-N-
(carbomethoxy)acetamidrazone;
(2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-1-
10 bis(carbomethoxy)methyl-2-phenylpiperidine;
(2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-1-
bis(carboxamido)methyl-2-phenylpiperidine;
(2S,3S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-1-
(N-methanesulfonyl)carboxamidomethyl)-2-phenylpiperidine;
15 and salts and prodrugs thereof.

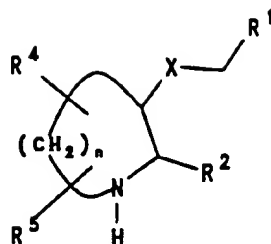
10. A compound as claimed in any preceding
claim for use in therapy.

- 20 11. A pharmaceutical composition comprising a
compound as claimed in any of claims 1 to 9 in
association with a pharmaceutically acceptable carrier.

12. A process for the preparation of a
25 compound as claimed in claim 1 which process comprises
(A) reacting a compound of formula (II):

30

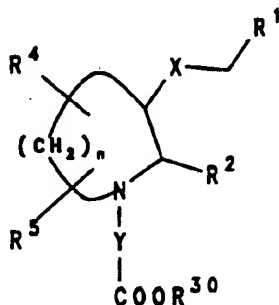
- 49 -



(II)

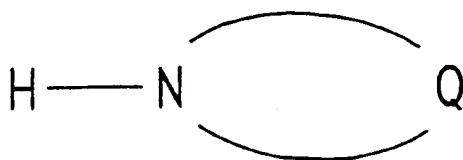
- 10 wherein R^1 , R^2 , R^4 , R^5 , X and n are as defined for formula (I) with a reagent suitable to introduce the group R^8 ; or

(B) reacting an intermediate of formula (III):



(III)

- 25 wherein R^1 , R^2 , R^4 , R^5 , X and n are as defined for formula (I), R^{30} is H or alkyl and Y represents C_{1-6} alkylidene with an amine of formula $HNR^aC_{1-6}alkylR^{12}$, $HNR^{13}C_{2-6}alkenyl$, $HNR^{13}C_{2-6}alkynyl$, $HNR^aC(NR^b)NR^cR^9$, $HNR^aheteroaryl$ or



in the presence of a base;

- 50 -

and optionally forming a salt or prodrug.

13. A method for the treatment or prevention
of a physiological disorder associated with an excess of
5 tachykinins, which method comprises administration to a
patient in need thereof of a tachykinin-reducing amount
of a compound according to claim 1.

14. A method according to claim 13 for the
10 treatment or prevention of pain or inflammation.

15. A method according to claim 13 for the
treatment or prevention of migraine.

16. A method according to claim 13 for the
15 treatment or prevention of arthritis.

17. The use of a compound as claimed in claim
1 for the manufacture of a medicament for the treatment
20 of a physiological disorder associated with an excess of
tachykinins.

18. The use of a compound as claimed in claim
1 for the manufacture of a medicament for the treatment
25 of pain or inflammation.

19. A compound as claimed in any of claims 1
to 10 when prepared by the process of claim 12.

20. A process for preparing a composition as
30 claimed in claim 11 which process comprises bringing a
compound as claimed in any of claims 1 to 9 into
association with a pharmaceutically acceptable carrier or
excipient.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 93/01525

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C07D211/42; A61K31/445;	C07D401/12; A61K31/40	C07D207/12; C07D211/54
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07D ; A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	EP,A,0 436 334 (PFIZER INC) 10 July 1991 cited in the application *see definitions of R6 and R8*	1-12, 17-20
P,X	EP,A,0 528 495 (MERCK SHARP & DOHME LTD.) 24 February 1993 cited in the application *see especially definition of R8 on page 4, line 27, i.e. alkyl substituted by COCONR10R11*	1,2,4-8, 10-12, 17-20
P,Y	---	1-12, 17-20
P,A	EP,A,0 499 313 (MERCK SHARPE & DOHME) 19 August 1992 ---	1-12, 17-20
	-/--	
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified).</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
09 NOVEMBER 1993	25. 11. 93	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	SCRUTON-EVANS I.	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P, Y	JOURNAL OF MEDICINAL CHEMISTRY vol. 35, no. 26, 1992, pages 4911 - 4913 'Discovery of a potent substance P antagonist: recognition of the key molecular determinant' ---	1-12, 17-20
X	CHEMICAL ABSTRACTS, vol. 100, 1984, Columbus, Ohio, US; abstract no. 192245m, 'The synthesis of peptide beta-lactams as potential protease inhibitors' page 619 ; see abstract & JOURNAL OF THE CHEMICAL SOCIETY., PERKIN TRANS 1 vol. 1, 1984, pages 29 - 39 *see compounds of formula I* -----	1,3,4,6, 7

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 9301525
SA 77499

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

09/11/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0436334	10-07-91	WO-A- 9109844	11-07-91
		EP-A- 0558156	01-09-93
EP-A-0528495	24-02-93	AU-A- 2413892	16-03-93
		WO-A- 9304040	04-03-93
EP-A-0499313	19-08-92	JP-A- 5078354	30-03-93
		US-A- 5242930	07-09-93
		CA-A- 2060949	12-08-92